GlaxoSmithKline	GSK1004723
Mechanism of Action	Histamine H1/H3 receptor antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=262&familyId=33 http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=33&objectId=264 http://www.ncbi.nlm.nih.gov/gene/3269; http://www.ncbi.nlm.nih.gov/gene/11255
Overview	GSK1004723 is a highly potent dual H1/H3 receptor antagonist designed for once-daily intranasal dosing. Non-clinical studies suggest that the long duration of action of GSK1004723 reflects slow dissociation from its target histamine receptors. Potent binding affinities for hH1 and hH3 receptors (pK_i = 10.0 and 10.8, respectively), and selective vs. human H2 or H4 receptors (both $pIC_{50} < 5.0$). This was confirmed in Ca2+ mobilization studies in CHO hH1 cells (pA_2= 8.9) and CHO hH3 cells (pA_2 = 9.6) with at least 800-fold selectivity vs. H2 and H4. Brain penetration was low in rats following intravenous administration. In studies using histamine-challenged human bronchus preparations, GSK1004723 exerted sustained (> 10 hours) antagonism following washout. A sustained 72-hour blockade of the upper airway response to intranasal histamine challenge was also seen in guinea pigs.
Safety/Tolerability	Toxicology assessment in rats and dogs (up to 4-weeks duration) led to mainly observations of intranasal and intravenous injection site irritancy. Other findings included minimal changes in the tracheo-bronchial lymph node and pituitary gland in rats. Genotoxicity assessments suggest that GSK1004723 does not present a genotoxic hazard to humans. hERG tail current was inhibited in HEK-293 hERG cells in a dose-dependent manner, with nominal IC_{25}, IC_{50} and IC_{75} values of 7.4, 20.3 and 55.4 ng/ml, respectively. However, there was no effect on QT or QTc intervals in dogs following a single IV dose of up to 1 mg/kg. There were no adverse effects on early embryonic development in rats, or on embryofetal development in rats and rabbits. Changes in estrus cycle duration and a reduction in fertility index were observed in rats. There was no evidence for potential effects on male fertility in rats. In humans, GSK1004723 was well tolerated with minimal systemic exposure when administered intranasally in single and repeat dosing (up to 1100 µg daily for two weeks).
Additional Information	GSK1004723 showed low levels of H1 antagonist activity and no evidence of reduced nasal congestion in single dose allergen challenge chamber studies (220 and 1100 µg, administered 2 hours after allergen challenge). The lack of activity may be due to the low solubility of the napadisylate salt suspension . GSK1004723 showed good H1 antagonist activity by reducing the symptoms of itching, sneezing and rhinorrhoea in repeat dosing with the dihydrochloride salt in allergen challenge chamber studies (1000 µg once daily for 3 days; last dose administered 1hour before allergen challenge). There was no evidence for reduced nasal congestion.
Suitable for and Exclusions	Maximum duration of dosing supported by toxicity studies: 28 days. Designed for intranasal once daily dosing; however, other topical routes may be possible with reformulation. Applications related to skin disease are of particular interest since GSK studies indicate significant expression of H3 receptors in human skin yet their functional and/or pathophysiological significance remains unclear.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=GSK1004723
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=GSK1004723